Arnold & Porter

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December 13, 2021

BY EMAIL

Office of Environmental Health Hazard
Assessment
1001 I Street, 12th Floor
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https://oehha.ca.gov/comments

Re: Comments on Notice of Proposed Rulemaking: Amendment to Section 25705 Specific Regulatory Levels Posing No Significant Risk (1,3-Dichloropropene)

To Whom It May Concern:

The following comments are submitted on behalf of The Dow Chemical Company ("Dow") in response to the October 29, 2021 Notice of Proposed Rulemaking: Amendment to Section 25705 Specific Regulatory Levels Posing No Significant Risk (1,3-Dichloropropene), which proposes to establish a regulatory default No Significant Risk Level ("NSRL") for 1,3-Dichloropropene ("1,3-D") of 3.7 micrograms per day by both the oral and inhalation routes of exposure. Because OEHHA's proposal is not a response to a need for greater clarity among the regulated community but instead an effort to support the goals of activists seeking to influence ongoing regulatory proceedings and court proceedings, and for the other reasons stated below, Dow opposes OEHHA's proposal.

I. It is Both Unnecessary and Inappropriate for OEHHA to Establish a Regulatory Default NSRL for 1,3-D.

OEHHA's purpose in establishing a regulatory default NSRL for a chemical is "to provide some 'safe harbor' levels and methodologies . . . which will assist persons in making certain that their . . . exposures pose no significant risk . . . within the meaning of" Proposition 65. Final Statement of Reasons, 22 California Code of Regulations Division 2 (June 1, 1989), at p. 4. In other words, OEHHA establishes these levels to

provide certainty to the regulated business community that exposures below the default NSRL are exempt from Proposition 65 warnings.

Dow is the sole manufacturer of products containing 1,3-D, and every package of 1,3-D sold or distributed for use in California bears an appropriate Proposition 65 warning for cancer. No business has requested that OEHHA issue a regulatory default NSRL for 1,3-D, and indeed every major trade association representing businesses who use 1,3-D in California has urged OEHHA not to proceed to establish such a regulatory default NSRL. *See* Letter to Cal-EPA Secretary Jared Blumenfeld from Almond Alliance of California, California Farm Bureau Federation, Western Growers Association, Western Plant Health Association, Western Agricultural Processors Association, California Pear Growers Association, Sacramento Valley Landowners Association, Agricultural Council of California, California Fresh Fruit Association, California Association of Winegrape Growers, California Sweetpotato Council, California Citrus Mutual, California Walnut Board & Commission, California Seed Association, American Pistachio Growers, and California Strawberry Commission (Aug. 19, 2019) (Exhibit 1).[1] It is virtually unprecedented for OEHHA to proceed to establish a regulatory default level for a chemical in the face of concreted opposition from the business community that is intended to be the beneficiary of the clarity provided by such a level, and there is no reason for OEHHA to deviate from its past practice here.

Indeed, the April 15, 2019, request for OEHHA to establish a regulatory default NSRL for 1,3-D came from Californians for Pesticide Reform, an organization that had two years earlier sued the California Department of Pesticide Regulation ("DPR") over its regulatory approach to 1,3-D exposures and that had secured a court judgment requiring DPR to revise its regulatory program for 1,3-D to address potential cancer risks to bystanders. *See Juana Vasquez, Californians for Pesticide Reform, and Pesticide Action Network North America v. California Department of Pesticide Regulation*, Alameda Superior Court No. RG17847563 (filed January 31, 2017; judgment entered May 14, 2018). In that litigation, a major issue was the differing views of DPR and OEHHA on the appropriate scientific method for evaluating the carcinogenicity of 1,3-D, namely whether it should be assessed using a portal-of-entry approach or a systemic approach. DPR's scientific evaluation of the data concluded that a portal-of-entry approach was appropriate; that approach would lead to an NSRL of 50 micrograms per day. OEHHA disagreed and favored a portal-of-entry approach, the same approach OEHHA has used in this proposed rulemaking, which results in a significantly lower NSRL. The judgment in the litigation emphasized the obligation of DPR to take account of OEHHA's views in accordance with Food & Agricultural Code sections 12980 and

[1] Dow hereby incorporates the comments of these trade associations.

12981. And at the time of Californians for Pesticide Reform's petition on April 15, 2019, DPR's process for revising its regulatory approach to 1,3-D was well underway. In fact, it is still underway.

Furthermore, the petition from Californians for Pesticide Reform was submitted by Howard Hirsch of the Lexington Law Group, who also represents another activist group, Center for Environmental Health, in its Proposition 65 enforcement action against Dow alleging failure to provide warnings for 1,3-D to residents of a community in Kern County. *See Center for Environmental Health v. Dow AgroSciences LLC*, Kern Superior Court No. BCV-18-100589 (filed September 20, 2016). At the time that the petition was submitted, and indeed to this day, that case is pending before the Kern Superior Court. In that litigation, the court will be called on to determine the appropriate NSRL for 1,3-D in order to determine whether exposures from Dow's sale of its pesticide products required a warning under Proposition 65.

This effort by OEHHA to weigh in on behalf of these activist groups and against the agricultural community by adopting its proposed regulatory default NSRL for 1,3-D will in any event be a waste of its resources. By OEHHA's own regulations, a regulatory default NSRL is set "solely for purposes of" Proposition 65 and cannot "be construed to establish or exposure or risk levels for other regulatory purposes." 27 Cal. Code Regs. § 25701(d). Furthermore, it does not "preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in [the OEHHA regulations] to establish that a level of exposure to a listed chemical poses no significant risk." 27 Cal. Code Regs. § 25701(a). In other words, the regulatory default NSRL proposed by OEHHA, if adopted, has no legal effect on either the DPR regulatory program or the Proposition 65 enforcement action against Dow.

OEHHA's proposal is therefore a highly questionable use of its limited resources. Just as the entire agricultural community urged OEHHA not to proceed to adopt a regulatory default NSRL for 1,3-D as sought by activist groups, Dow urges OEHHA to withdraw its proposal.

II. Because 1,3-D Was Listed Based Only on Gavage Data, no NSRL Can Be Established for the Inhalation Route of Exposure.

OEHHA proposed to establish a regulatory default NSRL for 1,3-D by two routes of exposure: inhalation and oral. But 1,3-D was listed by the State's Qualified Experts on the basis of gavage (oral exposure) data only. The State's Experts specifically excluded inhalation as the basis for listing. Therefore, it would be inappropriate to develop a regulatory default NSRL for exposures by inhalation because the inhalation

pathway is not relevant under Proposition 65. *See* The Dow Chemical Company Response to Request for Information Relevant to the Development of an NSRL for 1,3-D (May 25, 2021) (Exhibit 2), at pp. 2-4. [2] Dow has previously commented on this issue, and OEHHA has dismissed its comments summarily and refused its request for a meeting to discuss this issue. Dow therefore reiterates its comments here in hopes that OEHHA will consider them.

III. The Proposed Regulatory Default NSRL Is Based on Hyper-Conservative Assumptions and Faulty Methodology.

In arriving at its proposed regulatory default NSRL of 3.7 micrograms per day, OEHHA made multiple conservative assumptions, some of which are quite controversial and novel in the scientific community, and compounded these with faulty methodology. The nature of a regulatory default level under Proposition 65, however, is such that OEHHA believes it is entitled to use such a hyper-conservative approach, and Dow is under no illusion -- particularly in the context of this rulemaking as set out above -- that it will be able to persuade OEHHA to revise any of these assumptions. Dow therefore catalogs certain of these assumptions for the record so that policy makers and judicial officers who in the future will undoubtedly be called on to defer to or otherwise give credibility to OEHHA's default regulatory NSRL for 1,3-D will understand its limited usefulness.

Systemic vs. Portal-of-Entry Approach. As discussed above, scientists at the California Department of Pesticide Regulation, who have assessed 1,3-D in multiple contexts and immersed themselves for years in the data on this chemical, believe it is most appropriately assessed using the portal-of-entry approach. DPR's 2015 1,3-Dichloropropene Risk Characterization Document ("RCD") emphatically states that the weight of the evidence supports 1,3-D as a portal-of-entry carcinogen. OEHHA's use of a systemic approach accounts for more than a 3-fold difference in the default regulatory NSRL.

Cancer Slope Factor Based on Multiple Tumor Sites. In its risk assessment of 1,3-D, DPR based its inhalation cancer slope factor on the most sensitive tumor type in an animal study, which was lung bronchioloalveolar adenoma and carcinoma in male mice in the Stott et al. (1987) study. In contrast, OEHHA based its human inhalation cancer slope factor on multiple tumor sites, including bronchioloalveolar adenomas and carcinomas, as well as lacrimal gland cystadenoma and carcinoma in male mice in the

[2] Dow hereby incorporates these prior comments submitted in response to OEHHA's request for information in response to the petition of Californians for Pesticide Reform.

Stott et al. (1987) study. OEHHA did a similar analysis on oral exposure data. In essence, OEHHA "added up" the cancer slope factors for any tumors that it considered positive. This accounts for more than a 2-fold difference in the default regulatory NSRL.

Reduction in Denominator for Cancer Data. In developing the NSRLs for 1,3-D, OEHHA did not use the tumor incidences reported by Stott et al. (1987) and NTP (1985). Instead, OEHHA obtained the raw data and expressed the cancer data as the number of mice with tumors in the numerator and the number of mice alive at the appearance of the first tumor in the denominator. Usually, the denominator is the number of animals assigned to the study, not the number alive at the appearance of the first tumor. The lower the denominator, the higher the incidence of tumors and therefore the higher the cancer slope factor.

Linear Multistage Model. OEHHA used the linear multistage model in determining its proposed regulatory default NSRL. As noted in Dow's May 25, 2021 Response to Request for Information (at p. 5), in 2019 the U.S. Environmental Protection Agency, which regulates 1,3-D under the Federal Insecticide, Fungicide, and Rodenticide Act, recommended using a threshold-based point of departure for all forms of chronic toxicity (including cancer) associated with exposure to 1,3-D. EPA implemented this approach in its 2020 Registration Review of 1,3-D.

OEHHA used other highly conservative approaches that drove down its proposed regulatory default NSRL. Indeed, using the more realistic assumptions and methods employed by DPR would result in an NSRL of 50 micrograms per day, and using those employed by US EPA would result in an NSRL of 400 micrograms per day. *See* Dow's May 25, 2021 Response to Request for Information (at pp. 13-17).

OEHHA has multiple incentives to set the regulatory default levels very low using highly conservative assumptions and methodology. A regulatory default level essentially exempts exposures below that level from liability under Proposition 65. There may be good policy reasons to limit such exemptions, for example if there is uncertainty about the toxicity of a chemical. But such exemptions also draw criticism and sometimes litigation from activist groups who challenge the regulatory default levels as being too low. Businesses are less likely to file such challenges because they retain the right, under the statute and regulations, to establish that the true NSRL for the chemical is much higher than OEHHA's default regulatory level, based on different "evidence, standards, risk assessment methodologies, principles, assumptions or levels." 27 Cal. Code Regs. § 25701(a). Furthermore, it bears noting that OEHHA is the recipient of 75% of all civil penalties paid by alleged violators in Proposition 65 enforcement actions filed by private enforcers.

IV. OEHHA Should Abandon This Rulemaking or Revise It to Adopt a Regulatory Default NSRL of at Least 50 Micrograms Per Day.

For the reasons explained above and in the exhibits, OEHHA should abandon this effort to assist activist groups and withdraw its October 29, 2021 proposal. In the alternative, OEHHA should acknowledge the validity of the data and analysis submitted by Dow in its May 25, 2021 response to OEHHA's request for information. Based on that data and analysis, OEHHA should adopt a regulatory default NSRL for 1,3-D of at least 50 micrograms/day.

Should OEHHA proceed to adopt a regulatory default NSRL for 1,3-D, it should emphasize the limited effect of that regulation, as it has in other rulemakings, namely that it is "solely for purposes of" Proposition 65 and cannot "be construed to establish or exposure or risk levels for other regulatory purposes." 27 Cal. Code Regs. § 25701(d). And that it does not "preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in [the OEHHA regulations] to establish that a level of exposure to a listed chemical poses no significant risk." 27 Cal. Code Regs. § 25701(a). But regardless of whether OEHHA will note the narrow nature of its proposal, the law remains that it will have no legal effect on either the DPR regulatory program or the Proposition 65 enforcement action against Dow or other businesses that sell, distribute, or apply 1,3-D.

Sincerely,

Trenton H. Norris

Exhibit 1: Letter to Cal-EPA Secretary Jared Blumenfeld from Almond Alliance of California, California Farm Bureau Federation, Western Growers Association, Western Plant Health Association, Western Agricultural Processors Association, California Pear Growers Association, Sacramento Valley Landowners Association, Agricultural Council of California, California Fresh Fruit Association, California Association of Winegrape Growers, California Sweetpotato Council, California Citrus Mutual, California Walnut Board & Commission, California Seed Association, American Pistachio Growers, and California Strawberry Commission (Aug. 19, 2019)

Exhibit 2: The Dow Chemical Company Response to Request for Information Relevant to the Development of an NSRL for 1,3-D (May 25, 2021)

EXHIBIT 1

August 19, 2019

Dear Secretary Blumenfeld,

Our organizations represent farmers in California who grow fruits, nuts, vegetables, and other crops that are important to the state's agricultural economy. We are writing you regarding a petition pending before the Office of Environmental Health Hazard Assessment (OEHHA) concerning 1,3-dichloropropene (1,3-D), an essential tool our members use to protect their crops in the most difficult soil-pest management situations.

The petition filed with OEHHA threatens to usurp an administrative rulemaking proceeding by the Department of Pesticide Regulation (DPR) to develop new statewide regulations for soil fumigant products containing 1,3-D. By statute, DPR is the lead agency responsible for developing those regulations. DPR agreed to initiate the rulemaking proceedings in response to a May 2018 judgment by the Alameda County Superior Court, and we understand DPR's scientists are presently in the midst of a complex and highly technical analysis to ensure DPR's rulemaking satisfies all the statutory requirements. If the petition before OEHHA is granted, it would interfere with DPR's ongoing scientific analysis and disrupt the proper allocation of responsibility between DPR and OEHHA for the development of the new regulations. Moreover, it appears the petition was filed with OEHHA in an effort to drag that agency into litigation pending in Kern County concerning the alleged need for Proposition 65 warnings for 1,3-D applications.

Given that DPR and OEHHA are sister agencies within the California Environmental Protection Agency (Cal-EPA), we are hopeful you can intervene in this matter by discouraging OEHHA from giving further consideration to the

petition. OEHHA already will play a statutorily defined role in the development of the new regulations, including by consulting with DPR, as required by law, on certain issues relevant to human health. Granting the petition, by contrast, would undermine the collaborative inter-agency approach required by statute. Additionally, it would run afoul of the longstanding reluctance by CalEPA and its agencies to become embroiled in privately litigated matters, such as the Proposition 65 suit in Kern County.

Background Regarding 1,3-D

Soil fumigation is an integral part of farming operations throughout California and is fundamental to sustaining the state's agricultural economy. 1,3-D has been used in agriculture since the 1950s and has been extensively studied by various agencies worldwide. It is the active ingredient in soil fumigants that control nematodes, fungi, and other pests that otherwise would damage root structures of new plants. This not only helps boost crop yields, but also allows for more efficient use of water, fertilizers, and nutrients and less reliance on other pesticide products.

Unlike many other pesticides, 1,3-D products are not applied to plants or crops themselves. Instead, they are applied to the soil before crops are planted, at least 12 inches below the surface using a fumigant shank and then mechanically sealed or applied with a water-drip apparatus and then sealed in the soil with a plastic tarp. For plants with long lifespans like fruits, nuts and grapevines, only one application is typically needed, when new trees or vines are planted every 20 to 30 years.

General Regulatory Restrictions on 1,3-D

The distribution, sale, and use of products containing 1,3-D is extensively regulated at the federal, state, and county level. The Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA") prohibits the distribution of any chemical substance for pesticidal purposes without a federal registration, which the U.S. EPA only issues after a thorough examination of scientific data relevant to human-health concerns. FIFRA also imposes mandatory federal labeling requirements for 1,3-D products, including directions for how to safely handle and legally apply them.

At the state level, the Food and Agricultural Code requires DPR to perform a similarly exhaustive scientific analysis before registering 1,3-D products for lawful sale in California. Among other factors, DPR must evaluate the potential for acute and chronic toxicity (including carcinogenicity), including risks from inhalation. By statute, DPR also is required to continuously evaluate all registered pesticides, such as 1,3-D products, and where appropriate can impose use restrictions or other control/mitigation measures as conditions to their continued registration. DPR also is the lead agency responsible for adopting regulations governing pesticides and worker safety (e.g., field reentry times and protective devices), although DPR must consult with OEHHA and consider its recommendations when the proposed worker-safety regulations relate to health effects.

Additionally, because they are restricted use pesticides, 1,3-D products only may be applied by certified applicators who have permits from the County Agricultural Commissioners (CACs). Under the Food and Agricultural Code, the CACs must publish regulations governing the use of any restricted material they find may cause injury to the environment or to any person. Before any individual application of 1,3-D is allowed, moreover, the pertinent CAC must approve a notice of intent to apply after considering a host of factors, including local field conditions.

The Township Cap Program

Since 1999, the central component of DPR's regulatory approach to 1,3-D in California has been the "township cap" program. Among other use restrictions, this program limits the number of pounds of 1,3-D that can be applied per year in any given 6 x 6 square mile township. It was implemented by DPR as a condition on the continued registrations of 1,3-D products and has gradually evolved over time, as more robust data and improved scientific methods have become available.

The most recent changes to the program, effective in January 2017, were based on an exhaustive analysis of the most modern scientific data. This process started in 2015, when DPR began its updated risk assessment to reevaluate, using the newest data and techniques, the level of 1,3-D in the atmosphere that might result in a

significant risk of cancer for humans. This comprehensive analysis culminated in December 2015, when DPR issued a 275-page Risk Characterization Document (RCD) authored by a team of scientists within DPR's Human Health Assessment Branch.

In October 2016, based on the RCD's scientific conclusions, DPR announced a new Risk Management Directive (RMD) for 1,3-D. The RMD outlined the most restrictive set of control measures for the use of 1,3-D products anywhere in the world in order to protect people from possible cancer risks from trace airborne concentrations. In addition to adjusting the township cap and eliminating the prior "banking" system that had been in place since 2002, the RMD also endorsed a complete ban on 1,3-D applications in the month of December to account for seasonal weather conditions. Based on DPR's prior scientific analysis, the RMD concluded these mitigation measures would prevent the air concentration of 1,3-D from exceeding even half of the regulatory target of 0.56 parts per billion (ppb), thereby preventing any significant risk of cancer from airborne exposures.

At each stage of this process, DPR solicited and responded to comments from interested persons and other agencies, including OEHHA, the California Air Resources Board (CARB), and the U.S. EPA. In particular, OEHHA and the U.S. EPA provided detailed comments to the RCD, which DPR considered and responded to publicly. Likewise, OEHHA and CARB provided comments to the draft RMD that DPR circulated in August 2016, and DPR again made its responses publicly available. With respect to OEHHA's comments specifically, we understand DPR and OEHHA jointly consulted with your predecessor, Secretary Matt Rodriguez, who helped resolve certain disagreements between the two agencies concerning the appropriate airborne target concentration.

The Petition to OEHHA and the Related Litigation

The petition to OEHHA is an effort to effectively override DPR's thorough scientific analysis by asking OEHHA to declare a competing "no significant risk level," or NSRL, for 1,3-D.

Specifically, the petition was informally initiated by an email to OEHHA dated July 28, 2016, after DPR had finalized the aforementioned RCD. The email was submitted on behalf of Californians for Pesticide Reform and was copied to two other public-interest groups that also staunchly oppose pesticide use, including the Center for Environmental Health, but no one else.

The email noted that 1,3-D has appeared on California's Proposition 65 list since January 1998. This listing reflects California's prior determination that 1,3-D has carcinogenic effects, at least at certain excessive exposure levels. While the scientific validity of that conclusion is disputable, all products containing 1,3-D that are sold for use in California nevertheless include the requisite Proposition 65 warning, in both their federally approved labels and the accompanying Safety Data Sheets.

The July 2016 email requested OEHHA to establish a NSRL, also known as a "safe harbor" level, for 1,3-D and two other pesticidal chemicals. Normally, the statutory purpose of a NSRL is to provide clarity to manufacturers, sellers, and others regarding the level of a chemical that may be present before a Proposition 65 warning is required – an unnecessary request because a warning is already provided with the product.

Nevertheless, on August 5, 2016, OEHHA stated it would review the request expeditiously and that it was under consideration by OEHHA's senior management. This response, notably, was sent after OEHHA had commented on DPR's draft risk assessment and management documents (i.e., the RCD and RMD), but before the RMD was finalized and issued on October 6, 2016. After receiving a follow-up inquiry, OEHHA then stated, in a October 17, 2016 email, that it would establish a safe-harbor level for 1,3-D and the other chemicals referenced in the original email.

In January 2017, Californians for Pesticide Reform ("CPR"), filed a lawsuit against DPR in Alameda County Superior Court alleging that the RMD and the related changes to DPR's township cap program for 1,3-D constituted an

improper "underground regulation" and improperly disregarded OEHHA's prior comments regarding the proper target air concentration.

In other words, OEHHA had been led to agree to establish a NSRL for 1,3-D by an interested party, who then opportunistically filed a lawsuit against DPR based on alleged inter-agency conflicts between OEHHA and DPR. That lawsuit was not the only one implicating 1,3-D and the permissible level of airborne concentrations. In September 2016, shortly after OEHHA had agreed to consider the email petition, the Center for Environmental Health (CEH), filed a private Proposition 65 lawsuit in Alameda County alleging that individuals in Shafter, California had been exposed to allegedly unhealthy levels of 1,3-D without first receiving a Proposition 65 warning.

The petition effectively seeks to compel OEHHA to act on its prior advisement that it would set a NSRL for 1,3-D, notwithstanding OEHHA's apparent change of course in light of the intervening developments over the past three years. If OEHHA were to take such action now, it would have obvious implications for the Proposition 65 lawsuit, which is still pending and currently set for trial in May 2020.

DPR's Current Regulatory Rulemaking Activities

In May 2018, the Alameda County Superior Court issued a judgment and writ of mandate in the suit filed by CPR against DPR based on its alleged failure to follow OEHHA's recommendations. In those rulings, the Court concluded that DPR's most recent iteration of the township cap program was an improper "underground regulation" and ordered DPR to formulate new regulations concerning 1,3-D after complying with the formal rulemaking requirements of the California Administrative Procedure Act. Additionally, the Court directed DPR to comply with the Food and Agricultural Code, which require DPR to consult with OEHHA about health effects when formulating worker-safety pesticide regulations.

Because an intervenor appealed these rulings, DPR has taken the position that the Court-imposed time deadlines for the new regulatory rulemaking are stayed. Nevertheless, DPR agreed to voluntarily initiate the formal rulemaking procedures in accordance with the Court's findings. Based on this development, parties to the lawsuit agreed to stay the appeal while DPR moved forward with its regulatory rulemaking.

In a recent filing in the Court of Appeal, DPR advised that the scope of its anticipated 1,3-D regulations has been revised and expanded to address acute exposure risks from the use of 1,3-D, as well as cancer risks to bystanders. As DPR explained, it is now in the midst of the highly technical and scientifically complex process of integrating these issues in its proposed 1,3-D regulation, which includes consulting with OEHHA and CARB. To ensure compliance with all the applicable statutory requirements for the development of its new regulations, DPR now estimates that it will issue a notice of proposed rulemaking for 1,3-D in Summer 2020. In the meantime, DPR has advised that it intends to propose interim control measures for 1,3-D that are even more stringent than those imposed under the latest version of the township cap program.

Our Interest in the Petition and the Rulemaking

As leading organizations representing California agriculture, we have a strong interest in ensuring that the new proposed regulations regarding 1,3-D are developed through a comprehensive, consistent, and rigorous analysis of all available toxicology and risk-assessment science. A full accounting of the best available science must be the basis for the regulation of all crop protection products, including 1,3-D. Unless that happens, we fear the availability and utility of 1,3-D soil fumigants will be severely compromised to the detriment of our members and the State's economy.

To avoid such an outcome, all departments within CalEPA should pursue sound and internally consistent scientific approaches, thereby bringing clarity and predictability to the policy keeping these essential 1,3-D products available. Many of our members have made planting decisions and economic investments well into the future in reliance on the continued availability of 1,3-D products. For example, many almond trees are purchased years in advance based on the farmers' understanding that they would be able to protect those crops using 1,3-D soil fumigants.

We recognize and value CalEPA's responsibility to protect human health and the environment with respect to potential pesticide exposure. If the most up-to-date toxicology information from new 1,3-D studies is used, and the full capabilities of advanced technologies for characterizing fumigant emissions are applied, we are confident that 1,3-D use in California will continue to be protective to the health of workers who apply it and the people who live near fumigated fields. In short, with the aid of the most modern science, the new regulations that DPR is in the process of developing, with the input of OEHHA and other California agencies, can protect human health and the environment while, at the same time, ensuring the continued availability of 1,3-D products to the farmers who depend on them.

The petition before OEHHA threatens to upend this deliberate and thorough multi-agency regulatory process, simply to promote the aims of private litigants. If OEHHA were to grant the petition, it effectively would usurp the rulemaking process that DPR is already undertaking, as the designated lead agency, in conformity with the governing statutes and the rulings of the Alameda County Superior Court. The complex and comprehensive scientific analysis in which DPR is presently engaged – with appropriate consultation by OEHHA, could be mooted, contradicted, or thrown in doubt by a parallel determination, made by OEHHA only, regarding a discrete issue that is only relevant, if at all, to the Proposition 65 context. Such a result not only would run afoul of the applicable statutory scheme and the Superior Court's rulings, but also would undermine the consistency and predictability our members need to produce the healthy fruits, nuts and vegetables that feed Californians and families all over the world. It also would unnecessarily draw OEHHA into litigated matters that are still active, at both the appeal and trial court level.

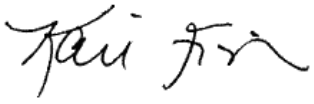
Conclusion

For these reasons, we urge Cal-EPA to intervene in this matter, as may be necessary, to discourage OEHHA from further considering or acting on the petition. Any such action by OEHHA would be both unnecessary and unwise, particularly given the far more comprehensive and thorough regulatory rulemaking proceeding in which DPR is presently engaged. If there is any additional information you would like from us or our members, please let us know and we will promptly provide it. In the meantime, we look forward to working with you to help keep California's agricultural economy strong while also protecting human health and the environment.

Sincerely,

Elaine Trevino
President
Almond Alliance of California

Michael Miiller
Director, Government Affairs
California Association of Winegrape Growers



Kari Fisher
Senior Counsel
California Farm Bureau Federation

Darren Barfield
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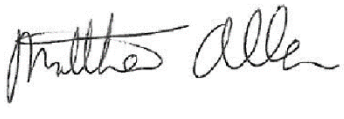

Matthew Allen
Director, California Government Affairs
Western Growers Association

Casey Creamer
President
California Citrus Mutual

Renee Pinel
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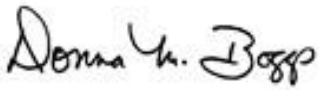
Western Plant Health Association

Michelle Connelly
CEO
California Walnut Board & Commission

Roger Isom
President/CEO
Western Agricultural Processors Association



Donna Boggs
Associate Director
California Seed Association

Debbie Murdock
Executive Officer
California Pear Growers Association

Sara Reid Herman
President
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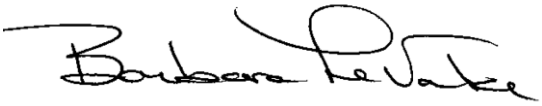

Barbara LeVake
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Tricia Geringer
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Mark Martinez
Vice President, Public Policy
California Strawberry Commission

Marcy L. Martin
Director, Trade
California Fresh Fruit Association

cc: Karen Ross, Secretary, California Department of Food and Agriculture
Val Dolcini, Department of Pesticide Regulation
Julie Henderson, California EPA
Bill Lyons, Office of Governor Gavin Newsom
Christine Hironaka, Office of Governor Gavin Newsom

EXHIBIT 2

Arnold&Porter

大成DENTONS

May 25, 2021

By Email

Office of Environmental Health Hazard Assessment
1001 I Street, 12th Floor
P.O. Box 4010
Sacramento, California 95812-4010
https://oehha.ca.gov/comments

Re: ***Response to Request for Information Relevant to the Development of a No Significant Risk Level for 1,3-Dichloropropene***

Sir or Madame:

On behalf of our client The Dow Chemical Company, we are submitting the attached *Response to Request for Information Relevant to the Development of a No Significant Risk Level for 1,3-Dichloropropene.* Pursuant to the instructions in the public notice[1] ("Notice") soliciting this submission, we are submitting this document to the Agency by electronic means. We ask that you please acknowledge OEHHA's timely receipt of these comments. Please note that we are providing paper copies as courtesy copies to Director Zeise, and to Carol Monahan-Cummings, OEHHA's chief legal counsel.

In preparing this Response, we observed that 1,3-D was listed by the State's Qualified Experts listing mechanism on the basis of gavage data only. The State's Experts specifically excluded inhalation as the basis for listing. Therefore, it would be inappropriate to develop an inhalation NSRL. Exposure by the inhalation pathway is not relevant under Proposition 65.

This issue—ensuring that the NSRL is consistent with the data that are the basis of listing—is a critical "gating" item that should be addressed before other submitters or OEHHA consider exposure by means other than gavage. *See* 27 Cal. Code Regs. § 25703(a) (quantitative risk assessment "shall be based on evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer"). Under the circumstances, we request that OEHHA withdraw and re-publish the Notice with this change. If OEHHA is disinclined, we request a meeting to determine what other curative steps the Agency may take.

Very truly yours,

Stanley W. Landfair
Dentons US LLP

Trenton H. Norris
Arnold & Porter

cc: Lauren Zeise, Director, OEHHA (U.S. Mail)
Carol Monahan-Cummings, Chief Counsel, OEHHA

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[1] Please refer to the OEHHA "Notice to Interested Parties Acceptance for Rulemaking and Request for Information Safe Harbor Level for 1,3-Dichloropropene" ("Notice"), March 12, 2021.

THE DOW CHEMICAL COMPANY

Response to

Request for Information

Relevant to the Development of a No Significant Risk Level

for

1, 3 - Dichloropropene

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May 25, 2021

THE DATA SUPPORT AN NSRL OF 50 MICROGRAMS PER DAY OR HIGHER

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RESPONSE TO REQUEST FOR INFORMATION
RELEVANT TO THE DEVELOPMENT OF AN NSRL FOR 1,3-D

The Dow Chemical Company (TDCC or Dow) submits the following in response to the Request for Information (Request) relevant to the development of a No Significant Risk Level (NSRL) for the chemical known as 1,3-Dichloroprene (1,3-D), issued by the Office of Environmental Health Hazard Assessment (OEHHA) on March 12, 2021.

THE DATA SUPPORT AN NSRL OF 50 MICROGRAMS PER DAY OR HIGHER

I. INTRODUCTION AND EXECUTIVE SUMMARY

OEHHA's Proposition 65 regulations provide that an NSRL must be based on "evidence and standards which form the scientific basis for listing." In this response, Dow submits studies, data and other information that meet this standard and are toxicologically relevant to develop and support an NSRL for 1,3-D. We demonstrate that the data support an NSRL of 50 micrograms per day (mcg/day) or higher. There are several valid routes to reach that result, and we have summarized below the bodies of evidence that we believe OEHHA should consider. A table at the end of this Introduction shows calculations of NSRLs at 50, 400, and 270-3100 mcg/day. The data support any of these values as NSRLs, depending on various factors that OEHHA may consider under the regulations, and should consider here.

The NSRL Must Be Consistent with the Data That Were the Basis of the Listing. In Section II of this submission, we demonstrate that 1,3-D was listed by the oral route, and not by inhalation. The decision to list 1,3-D was made in 1989 by the Scientific Advisory Panel (SAP) pursuant to the State's Qualified Experts (SQE) listing mechanism. The transcript of the December 1989 SAP meeting shows that the SAP listed 1,3-D expressly and exclusively on the basis of gavage data, by the oral route of exposure, and "not on the basis of inhalation." The data thus restrict the basis for listing to oral exposure, and rule out listing on the basis of inhalation. Given the established patterns of use, there is no significant oral exposure. Therefore, it is questionable whether any NSRL is appropriate, on the basis of the data. Nevertheless, in the event that OEHHA believes that the listing by the SQE for 1,3-D properly includes the inhalation route, we have developed NSRLs based on the data that are presently available.

The DPR and US EPA Risk Assessments Are Relevant. In Section III, we have analyzed risk assessments conducted by the Department of Pesticide Regulation (DPR) and the US Environmental Protection Agency (US EPA). Their risk assessments both identify exposures that present "no significant risk of cancer," as the regulations define that term. Both risk assessments are therefore relevant to developing an NSRL for 1,3-D. The compound has a long history of regulation as a pesticide by DPR and US EPA, and has been studied intensively by other governmental and academic institutions. The risk assessments were conducted recently and are supported by data from studies designed to measure and evaluate any risk of cancer that might arise from the use of 1,3-D products.

Studies That Suggest That Exposure to 1,3-D Does Not Present a Significant Risk of Cancer Are Relevant. In Section IV, Dow presents published, peer-reviewed studies suggesting that exposure to 1,3-D does not result in a significant risk of cancer. These data include: favorable genotoxicity and carcinogenicity studies; an inhalation toxicokinetic study demonstrating a threshold mechanism, such that a linearized, no-threshold approach to quantitative cancer risk assessment is not appropriate for 1-3-D; a comprehensive published synthesis of the recently

developed data; and the published findings of an independent panel which concluded that a threshold approach for quantitative cancer risk assessment is scientifically appropriate.

Data that DPR and US EPA Relied On and Support a Threshold Approach Are Relevant. Section V summarizes compelling data to support two alternate threshold approaches. The first would result in an NSRL of 400 mcg/day, based on US EPA's Cancer Assessment Review Committee (CARC) recommendation that a non-linear approach will adequately protect against carcinogenicity that could result from exposure to 1,3-D, as described in Section VII.C. The second approach would result in NSRLs ranging from 270 to 3100 mcg/day, using the $BMDL_{01}$ for lung tumors and applying appropriate uncertainty factors, as described in Section VIII.

Data that DPR and EPA Relied On and Support a Portal of Entry Approach Are Relevant. In 2016, in another setting, OEHHA opposed the use of a portal-of-entry approach. Section VI presents evidence to support a portal of entry approach and responds to OEHHA's earlier comments criticizing the approach.

The DPR Risk Assessment Yields an NSRL of 50 Micrograms Per Day. . Section VI. A presents an NSRL of 50 mcg/day, based on DPR's cancer risk assessment of 1,3-D and using a no-threshold approach (linear multistage model) and an RGDR factor based on portal-of-entry effects.

Potential NSRLs for 1,3-D, as set forth in this submission, are summarized in Table 1.

Table 1. Summary of potential NSRLs for 1,3-D

Basis for NSRL	Approach	NSRL (mcg/day
DPR risk assessment (2015)	Non-threshold (linear multistage model)	50
US EPA CARC review (2019)	Threshold (RfC)	400
$BMDL_{01}$ for lung tumors and uncertainty factors	Threshold ($BMDL_{01}$)	270 to 3100

II. The NSRL Must Be Consistent with the Data That Are the Basis of the Listing

A. The State's Qualified Experts Listed 1,3-D on the Basis of Gavage Data

1,3-D was listed as a chemical "known to the state" to cause cancer on January 1, 1989, *via* the State's Qualified Experts Listing Mechanism. The panel of experts (referred to then as the Scientific Advisory Panel or SAP) evaluated 1,3-D two weeks earlier at its December 16, 1988 meeting, held in Davis, California. It is clear from the meeting transcript that 1,3-D was listed on the basis of gavage data, not on the basis of inhalation. Pages 193-198 of the transcript include the Panel's discussion.

The discussion was led by Panel Member Dr. Warner North. According to the transcript, the concluding portion of the Panel's evaluation of 1,3-D states:

PANEL MEMBER NORTH: "So my recommendation is to list it."

CHAIRMAN KILGORE:	"With no—"
PANEL MEMBER NORTH:	"I think the record should show that ***we listed it based on the gavage data; not on the basis of inhalation.***" (Emphasis added.)
CHAIRMAN KILGORE:	"Okay. Any other comments? Disagreements? If not, ***it will be listed under those circumstances.***"[1] (Emphasis added.)

It was customary in the early years of Proposition 65 for the SAP to list a chemical by a "voice vote," without a show of hands. All decisions to list were considered unanimous unless objections were raised. Occasionally, members would disagree with the majority or recuse themselves from voting, and the transcript would reflect such circumstances. But, in the case of 1,3-D, no member of the SAP disagreed with the decision to list on the basis of gavage data, not on the basis of inhalation. It was a unanimous decision.

B. Exposure By The Inhalation Pathway Is Not Relevant Under Proposition 65

It is clear from the transcript that the SAP listed 1,3-D by the oral[2] route. The Proposition 65 list, as currently published, does not ***show*** the listing as restricted. Nevertheless, the listing ***is*** restricted (to the oral route), because the decision to restrict it was made by the State's Qualified Experts, and no agency has authority to overrule or second-guess the SAP's decision. The listing was published by the Health and Welfare Agency on January 1, 1989, before Cal/EPA and OEHHA were established. Since 1,3-D was listed by the SAP by the oral route only, exposure to 1,3-D by the inhalation pathway is not relevant.

It is also noteworthy that US EPA's Carcinogen Assessment Review Committee (CARC) reached a similar conclusion in 2019, based on a more complete data set that included all of the more recent carcinogenicity studies in animals that were not available to the SAP in 1988. The CARC concluded that there were no treatment-related tumors in male or female rats or female mice *via* the inhalation route, or in male mice *via* the inhalation route, at concentrations below the kinetically derived maximum tolerated dose (KMD).[3] Notwithstanding these findings, "the CARC classified 1,3-D (Telone) as 'Suggestive Evidence of Carcinogenic Potential' based on the

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[1] Transcript of the December 16, 1988 Meeting of the Proposition 65 Scientific Advisory Panel, p. 198.

[2] While the Scientific Advisory Panel used the term "gavage" rather than "oral," it is important to recognize that the only oral studies available at the time of its evaluation were the NTP bioassays of gavage administration of 1,3-D to mice and rats. At the time, there were no dietary carcinogenicity studies of 1,3-D.

[3] US EPA CARC (2019) Evaluation of the Carcinogenic Potential of 1,3-Dichloropropene. Cancer Assessment Document. September 26, 2019, p. 4-5.

presence of liver tumors by the oral route in male rats only."[4] In other words, US EPA's cancer classification of 1,3-D in 2019 is based on oral data, not inhalation data.

C. An Inhalation NSRL Is Not Appropriate Because the Inhalation Route of Exposure Was Specifically Excluded As the Basis for Listing

It is not possible to establish an inhalation NSRL, because 1,3-D is listed on the basis of oral exposure, and is not listed on the basis of inhalation. The Proposition 65 regulations require that an NSRL shall be based on the evidence which forms the basis for the listing. Specifically, the regulations state:

> "25703. Quantitative Risk Assessment
>
> A quantitative risk assessment which conforms to this section shall be deemed to determine the level of exposure to a listed chemical which, assuming daily exposure at that level, poses no significant risk. ***The assessment shall be based on evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer.*** . . . "[5]

27 Cal. Code Regs § 25703(a) (emphasis added).

As described in the transcript, 1,3-D was listed "based on the gavage data; not on the basis of inhalation." Therefore, any NSRL for 1,3-D must be based on oral exposure. And an inhalation NSRL cannot be established, for two reasons: (1) the listing of 1,3-D is restricted to the oral route of exposure and specifically excludes inhalation, and (2) the regulations require that the NSRL be based on evidence that formed the scientific basis for the listing, which is limited to oral data. Thus, an inhalation NSRL cannot be legitimately established for 1,3-D. Nevertheless, in the event that OEHHA disagrees and determines that 1,3-D was listed by the SAP by the inhalation route, information is provided in the following sections of this submission to assist OEHHA in proposing a scientifically defensible NSRL for inhaled 1,3-D.

Since 1,3-D was listed on the basis of oral data, it is possible to establish an oral NSRL. However, oral exposure to 1,3-D is negligible, and has not been identified as a concern by regulatory agencies, as demonstrated by the conclusions in DPR (2015) and US EPA (2019, 2020).

III. The DPR and US EPA Risk Assessments Are Relevant

A. DPR Concluded That 1,3-D Is A Portal-of-Entry Carcinogen

DPR published a risk assessment for 1,3-D in 2015. The document, referred to as the 1,3-Dichloropropene Risk Characterization Document (RCD) (DPR 2015), characterizes 1,3-D as a

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4 *Id.*, p. 5.

5 Title 3, California Code of Regulations, Section 25703(a).

lung tumorigen and states that the weight of the evidence supports 1,3-D as a portal of entry carcinogen:

> "...we felt ultimately that the evidence tilted to the portal of entry scenario. The following observations were marshalled in support of portal of entry: (a) upper respiratory irritation occurred after acute, subchronic and chronic exposure in rodents (Cracknell *et al.*, 1987; Nitschke *et al.*, 1990b) and after acute exposure in humans . . . ; in addition, rats decreased their breathing rate at 90 ppm (Stott and Kastl, 1986), which was interpreted as evidence for sensory irritation in the upper respiratory tract; (b) pharmacokinetic studies in rats showed definitively that inspired 1,3-D reaches the lower respiratory system (Stott and Kastl, 1986); (c) 1,3-D causes tumors on contact in other mouse tissues, including forestomach upon gavage exposure and skin (papillomas) upon dermal exposure (NTP, 1985); (d) skin sensitization resulted after dermal exposure in guinea pigs (Jeffrey, 1987); (e) oral, but not inhalation, exposure in rats caused liver adenomas, suggesting that local mechanisms were operative for liver tumors (Stott *et al.*, 1995)."

B. US EPA Reexamined The Data And Found Less Cause For Concern

1,3-D was designated as a carcinogen by US EPA's Office of Research and Development in 2000, in support of its Integrated Risk Information System (IRIS) (US EPA 2000). The agency initially classified 1,3-D as "likely to be carcinogenic to humans."

In 2019, the US EPA CARC reevaluated the carcinogenic potential of 1,3-D, based on the new and existing data, and downgraded its classification to "Suggestive Evidence of Carcinogenic Potential" (US EPA 2019). At the same time, US EPA recommended using a threshold-based point of departure (POD) for all forms of chronic toxicity.

Based on its reclassification of 1,3-D, US EPA concluded that "*quantification of human cancer risk is not required*" and recommended that a threshold-based approach will adequately account for all chronic toxicity, including carcinogenicity, that could result from long-term exposure to 1,3-dichloropropene (US EPA 2019). EPA implemented this approach in its recent 1,3-D Registration Review (US EPA 2020).

In addition, the CARC reviewed recently-generated inhalation data on the topic of kinetically-derived maximum tolerated dose (KMD) and stated the following: "CARC's conclusion on the exceedance of a kinetically derived maximum tolerated dose (KMD): The CARC concluded that based on the agency's independent evaluation and validation of the hockey-stick model, there is high confidence that the relationship between 1,3-D concentration in male mice blood and inhalation exposure was non-linear (and non-proportional) at exposure levels of 40 ppm and above. This supports that the concentration where benign lung adenomas were observed in male mice exceeded the KMD" (US EPA 2019).

Finally, the CARC assessed the genotoxicity data available for 1,3-D and concluded that "Based on a weight of evidence [review] of the available data and clear negative findings for

mutagenicity *in vivo*, the CARC concluded that 1,3-D is not a mutagenic concern *in vivo*." (US EPA 2019).

IV. Studies That Suggest that Exposure to 1,3-D Does Not Present a Significant Risk of Cancer Are Relevant

This section describes a variety of studies and recent evaluations that are highly relevant to the potential need for, and approach that may be associated with, an NSRL. Genotoxicity (Badding *et al.*, 2020) studies and carcinogenicity studies (Kelly, 1997; Kelly 1998) demonstrate that 1,3-D is negative for genotoxicity and is associated with limited tumorigenicity in laboratory animals, only at exposures significantly higher than concentrations measured in ambient air or water. (Yan *et al,* 2020: US EPA 2020). In addition, a recently conducted inhalation toxicokinetic study (Bartels *et al.*, 2020) clearly demonstrates that tumorigenicity associated with inhalation exposure to 1,3-D in male mice (Lomax, 1987; Lomax et al., 1989) operates through a threshold mechanism and as such, a linearized, no-threshold approach to quantitative cancer risk assessment is not appropriate.

A comprehensive synthesis of the recently developed data has been evaluated in a weight-of-evidence analysis and recently published (Yan *et al.*, 2020). Furthermore, an independent panel has reviewed the recent scientific developments for 1,3-D described by Yan *et al.* (2020) and published its findings and conclusions (Hays *et al.*, 2020). These data are presented largely as reprinted abstracts in Appendix A. We encourage OEHHA to review the studies and subsequent peer-reviewed publications.

It is important to understand the interrelationship of these new studies, as well as how they collectively question the need for a NSRL; which studies are most appropriate if an NSRL is to be derived; and the approach for developing the NSRL that best represents the science. The overall negative genotoxicity database for 1,3-D aligns with the majority of oncogenicity studies that are negative for tumorigenicity, indicating that 1,3-D is not a genotoxic carcinogen. The observation of a defined KMD in the inhalation toxicokinetic study supports a threshold approach for quantitative risk assessment and the absence of lung toxicity in all oral bioassays support the perspective that any observed tumors following inhalation exposure are associated with a portal of entry effect/mechanism.

V. Data That Support Using A Threshold Approach Are Relevant

In the US, 1,3-D was historically classified by the US EPA as "likely to be carcinogenic to humans." (US EPA 2000). Using the proposed cancer risk assessment guidelines at that time (*i.e.*, U.S. EPA, 1996), the Agency found that the weight of evidence for evaluation of cancer hazard suggested that 1,3-dichloropropene is "likely to be carcinogenic to humans." (US EPA 2000). The lack of mode-of-action data to support a nonlinear mechanism required the quantitative cancer assessment to assume a linear dose response.

Information and additional studies that have become available since then reveal now a different picture of the tumorigenic potential of the compound. These data and information include: (1) initial cancer studies by the NTP were conducted on an obsolete 1,3-D product that contained a known mutagen/carcinogen, epichlorohydrin, as a stabilizer, while current 1,3-D fumigants use epoxidized soybean oil (ESO) as the stabilizer; (2) results from two additional oral

rodent cancer bioassays conducted on the current 1,3-D product show a lack of carcinogenicity; (3) a newly conducted Big Blue study in F344 rats *via* the oral route further confirms that 1,3-D is not an *in vivo* genotoxicant; and (4) a newly conducted repeat dose inhalation toxicokinetic (TK) study showing that linear dose proportionality is observed below 30 ppm, demonstrates the non-relevance of 60 ppm 1,3-D-induced benign lung tumors in male mice for human health risk assessment.

A synthesis of these additional data supports the conclusion that 1,3-D is not a tumorigen at doses below 12.5 mg/kg bw/day *via* the oral route, or at concentrations below 30 ppm *via* the inhalation route. These findings and PODs show that a linear low dose extrapolation approach is not appropriate and a threshold-based risk assessment for 1,3-D is protective of human health.

Finally, in 2019, the CARC (US EPA 2019) reevaluated the carcinogenic potential of 1,3-D. In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (US EPA 2005), the CARC classified 1,3-D as presenting "Suggestive Evidence of Carcinogenic Potential based on the presence of liver tumors by the oral route in male rats only." Given this finding, EPA stated that "quantification of human cancer risk is not required. The CARC recommends using a non-linear approach (*i.e.* reference dose (RfD) that will adequately account for all chronic toxicity including carcinogenicity, that could result from exposure to 1,3-dichloropropene."

A. 1,3-D Is Not Genotoxic

There is an extensive body of literature on the *in vitro* and *in vivo* genotoxicity of 1,3-D. Many of these studies were reviewed by Stott *et al.* (2001). In the same way that the NTP carcinogenicity studies are compromised, results from most, if not all, of the early genotoxicity studies were confounded by the use of low purity and/or uncharacterized test material, often containing the known genotoxic stabilizing agent epichlorohydrin.

1. *In vitro* findings

Several of the *in vitro* studies were confounded when researchers, attempting to purify 1,3-D in the laboratory, generated mutagenic artifacts during the process that invalidated their findings. Nonetheless, some *in vitro* assays did identify a relatively restricted *in vitro* genotoxic activity for 1,3-D, but they are considered not relevant to *in vivo* situations or to the very low human occupational or ambient environmental exposure levels. Of particular interest in this context is the protective role, which has been demonstrated experimentally, provided by the addition of normal physiological levels of glutathione (GSH) to these *in vitro* systems (Klaunig *et al.*, 2015). In effect, the GSH reduces the genotoxic response observed in some of these *in vitro* assays and calls into question the relevance of even the positive *in vitro* findings for *in vivo* risk assessment.

2. *In vivo* findings

The database of 1,3-D *in vivo* guideline genotoxicity studies extends beyond what is required for pesticide registration and addresses the relevant genotoxicity endpoints of interest in a comprehensive manner. The results of the *in vivo* battery are of significant relevance in terms of assessing human hazard and risk and are also more robust and reliable given the limitations of the *in vitro* studies outlined above. Some "positive" *in vivo* genotoxicity studies on 1,3-D have

been published. Specifically, the *in vivo* studies that were positive—induction of micronuclei or chromosome aberrations—are compromised by the presence of 1% epichlorohydrin (Shelby *et al.,* 1993) or had an inadequate study design (*i.e.,* single animal in the vehicle control group (Kevekordes *et al.*, 1996).

In addition, several DNA fragmentation assays have been conducted at relatively high doses with "positive" findings. These studies suffer from basic methodological problems related to generation of artifacts secondary to cytotoxicity, lack of information about epoxide stabilizer in the test material, and general inconsistency between studies. Dr. Errol Zeiger, an internationally renowned genetic toxicologist, provided an independent expert opinion on the weight of evidence for the *in vivo* genotoxicity of 1,3-D (Zeiger, 2005) and concluded that the genetic damage induced by 1,3-D in rats and mice was limited to only non-specific DNA strand breakage which was not the result of direct DNA interaction.

It is particularly important to note that the *in vivo* mutagenic potential of 1,3-D has been assessed in the Big Blue mouse model. This assay represents the current state of the art approach for assessing in vivo mutagenicity in target organs or tissues. In this study, the mutagenic potential of 1,3-D was assessed in the relevant target organs (lung and also liver) at and above the *in vivo* tumorigenic dose. The authors concluded that 1,3-D was clearly non-mutagenic in the target organs of interest.

Thus, despite evidence for some positive genotoxicity findings in *in vitro* test systems that are ill equipped to detoxify 1,3-D, it has no such activity *in vivo* and was clearly non-genotoxic. Some of the relevant *in vivo* genotoxicity studies are included in Table 2 below (from Yan *et al* 2020).

Table 2. *In vivo* genotoxicity results.

Assay/exposure route	Species/strain/duration	Dose and examined tissue	Results
Mouse micronucleus/oral[b]	Mouse/CD-1/24 and 48 h	0, 38, 115, 380[a] mkd; bone marrow	Negative
Big Blue mouse/inhalation[c]	Mouse/B6C3F1/2 weeks	0, 10, 60, and 150 ppm; lung and liver	Negative in tumor target tissues
^{32}P-post labeling assay/oral and inhalation[d]	Rat/F344/up to 12 d Mouse/B6C3F1/up to 12 d	0, 5, 12.5, 25, and 100 mkd for oral route; liver 0, 10, 30, 60, and 150 ppm for inhalation route; lung	Negative in tumor target tissues
Dominant lethal assay/inhalation[e]	Rat/CD/10 weeks	0, 10, 60, and 150 ppm; NA	Negative for induction of dominant lethal mutations
Big Blue rat/oral[f]	Rat/F344/28 d	0, 12.5, 25, and 50 mkd; liverand kidney	

[a]The doses in bold are equal to or above the doses/concentrations causing observed tumors.
[b]Gollapudi et al., 1998, B.6.4.2.2 of Spain (2018), and Badding et al. (2020).[c]Gollapudi, 1997, B.6.4.2.1 of Spain (2018) and Badding et al. (2020). [d]Stott, 1997, B.6.8.2.5 of Spain (2018) and Badding et al. (2020). [e]Gollapudi, 1997, B.6.4.3.2 of Spain (2018) and Gollapudi et al. (1998). [f]Badding et al. (2020).

Finally, the CARC assessed the genotoxicity data available for 1,3-D and concluded that "Based on a weight of evidence of the available data and clear negative findings for mutagenicity *in vivo*, the CARC concluded that 1,3-D is not a mutagenic concern *in vivo*."

B. The Pattern of Tumors Is Inconsistent With a Genotoxic Carcinogen

The general lack of genotoxicity of 1,3-D *in vivo* is also consistent with the development of small, benign tumors in rats and mice relatively late in life. In addition, tumors in the dietary and inhalation bioassays of 1,3-D occurred only in tissues having either an extensive geriatric development of foci of altered cells, as in the livers of F344 rats, or a high spontaneous incidence of tumors, as in the lungs of B6C3F1 mice.

In normal animal models, chemicals causing tumors *via* this mode of action are well-recognized as requiring chronic administration, and their immediate effects display reversibility and are threshold events. The observation of an increased incidence of late-developing foci and tumor development in the dietary rat bioassay (Stott *et al.,* 1995) of 1,3-D also supports these findings. Foci of altered cells may thus reflect a measurable precursor event in tumor formation in rat liver. Further, as foci of altered cells are typically not as prevalent in the livers of Sprague-Dawley derived strains of rats as in Fischer 344 strain rats, these findings may also explain the lack of liver tumors in the more recent oral gavage bioassay of 1,3-D in rats (Kelly, 1998). The occurrence of initiated cells in the lungs of male B6C3F1 mice is evidenced by the relatively high spontaneous tumor incidence, on average approximately 20%, seen in controls of this strain. (Dixon *et al.*, 2008).

Consistent with enhancement of common late-developing tumors, recent work has demonstrated that 1,3-D exhibits a non-genotoxic mode of tumorigenic action in the rat liver and mouse lung by promoting the development of adenomas from spontaneously initiated cells within these tissues (Klaunig *et al.*, 2015). In the rat liver, this response involved the apparent route and strain-dependent clonal expansion of initiated cells to form visible foci and subsequently a low incidence of hepatocellular adenomas. In the mouse lung this involved the clonal expansion of initiated cells occurring spontaneously in this tissue. Promotion of spontaneously initiated cells to form tumors is a generally well accepted non-genotoxic mode of action (MOA) which displays both reversibility and practical thresholds. Metabolism and toxicokinetic data indicate that a significant genotoxic event would only be likely to occur at acutely life-threatening exposure levels *in vivo* that saturate normal defense mechanisms.

Evaluations of the available repeat-dose studies/interim examinations in F344 rats covering different exposure durations (90-day, 1-year, and 2-year) were conducted for liver effects. There were no treatment-related preneoplastic liver effects (such as liver cell hypertrophy, hyperplasia, necrosis, or inflammation) before liver foci and benign hepatocellular adenomas were observed. No tumors were observed at the 1-year interim histopathological examination, an indication of late onset relative to tumor formation. Furthermore, only benign tumors were induced with no indications of progression to malignancy following 2-year exposure at any exposure level (Stott *et al.,* 1995).

Further examination of the three other rodent cancer bioassays *via* oral exposure (Redmond *et al.*, 1995; Kelly, 1997; Kelly, 1998) was conducted to fully evaluate potential liver toxicity associated with 1,3-D. There was no association between exposure and liver tumor formation, nor was there a showing of causation between exposure and preneoplastic liver effects, as indicated by the absence of effects on liver weight, enzyme activity, or histopathology.

Additional evaluations of liver effects from two inhalation cancer bioassays demonstrate that the liver is only minimally affected with no biological or toxicological significance. These results provide evidence that the rodent liver is not a target organ of 1,3-D and the only evidence of liver tumorigenicity was in F344 rats at a dose level which exceeded the MTD.

In summary, collective analysis of the limited and scattered pattern of tumors across multiple cancer bioassays supports the view that 1,3-D is not a genotoxic carcinogen.

C. The Pharmacokinetics of 1,3-D Are Consistent with a Threshold Approach

With the understanding that blood concentrations of 1,3-D are representative of tissue exposures to this chemical, the available data provide multiple lines of evidence that systemic exposures to 1,3-D in the mouse become nonlinear at air concentrations of 30 ppm or above (Bartels *et al.*, 2020).

The GSH-dependent metabolism of 1,3-D results in significant depletion of GSH at repeated exposure levels of 30 ppm or above (Stott *et al.*, 2001). This loss of GSH then results in decreased metabolic clearance of this test material, with a concomitant increase in the 1,3-D isomers in circulating blood, and subsequently in tissues as well, at exposure to air concentrations above 30 ppm. The phenomenon was also shown to occur with 1,3-D in rats *via* GSH depletion with diethyl maleate (Yang, 1989).

Bartels *et al* (2020) investigated whether lung tumors observed in high dose male mice (Lomax 1987) are due to saturation of metabolic clearance. Results of this experimentation (see full description in Appendix A) provide multiple lines of evidence that systemic exposures to 1,3-D in the mouse become nonlinear at inhalation exposure levels of 30 ppm or above. A reduction in minute volume occurred at the highest exposure concentration. The glutathione dependent metabolism of 1,3-D results in significant depletion of glutathione (GSH) at repeated exposure levels of 30 ppm and above. This loss of GSH results in decreased metabolic clearance of this test material, with a concomitant increase of the 1,3-D isomers in circulating blood at exposure concentrations $\geq$ 30 ppm. Shifts in the ratio of cis- and trans-1,3-D also support nonlinear toxicokinetics well below 60 ppm.

The Bartels *et al.* (2020) data support a KMD for 1,3-D in mice at about 30 ppm. Statistical analyses indicated blood concentrations were proportional to exposure up to the range of 27–29 ppm 1,3-D. Above this range, probable saturation of GSH-based metabolic clearance leads to the supralinear increase in systemic exposure. These results support the non-relevance of benign pulmonary tumorigenicity, seen only at the highest (60 ppm) inhalation exposure in the male mouse inhalation bioassay (Lomax 1987), to human health risk assessment. This conclusion, coupled with the absence of adverse lung effects in five other cancer bioassays (in both rats and mouse *via* both inhalation and oral routes) (Kelly, 1997, 1998; Lomax *et al.*, 1989; Redmond *et al.*, 1995; Stott *et al.*, 1995) supports the observation that 1,3-D is not tumorigenic at concentrations below 30 ppm. These results support the non-relevance of 1,3-D-induced benign pulmonary tumorigenicity in mice for human health risk assessment.

VI. Data That DPR and US EPA Relied On and Support a Portal of Entry Approach Are Relevant

In a September 20, 2016 memorandum[6] commenting on DPR's draft Risk Management Directive for 1,3-D, OEHHA criticized the portal-of-entry approach. OEHHA commented that 1,3-D could not act through a portal of entry approach because gavage exposure to 1,3-D in male mice in the NTP cancer bioassay was associated with an increase in lung tumors. OEHHA took the position that the amount of epichlorohydrin in the test material (1% of test material) used by NTP was too low to explain the lung tumor response in male mice following inhalation exposure. While this perhaps is an area of scientific debate, there is clear evidence and consensus from multiple sources, including NTP (1985) and published reviews such as Giri (1997), that epichlorohydrin is mutagenic and genotoxic. Additionally, epichlorohydrin has been found to be carcinogenic in animal models (Van Duuren *et al.*, 1974; Konishi *et al.*, 1980; Laskin *et al.*, 1980). At the least, therefore, it is clear that the presence of epichlorohydrin in the NTP gavage bioassay was a confounding variable and may have certainly influenced the increase in lung adenomas.

Equally relevant to the present discussion are the numerous factors and study design elements that complicate and confound the NTP oral gavage study in mice, including the following:

> (1) In both studies, the test material, containing 1% epichlorohydrin as a stabilizer, was not representative of 1,3-D as currently manufactured. Epichlorohydrin is recognized as a mutagen and carcinogen (US EPA, 1984). The compound has been demonstrated to be mutagenic in both prokaryotic and eukaryotic systems, resulting in gene mutations in bacteria and cultured mammalian cells, sister-chromatid exchanges in human cells *in vitro* and chromosomal effects in both *in vivo* and *in vitro* mammalian assays (US EPA, 1984).
>
> (2) The evidence of carcinogenicity of epichlorohydrin includes nasal carcinomas in rats, local sarcomas in mice and forestomach neoplasms in rats. Konishi *et al.* (1980) reported that male Wistar rats offered epichlorohydrin in drinking water for 81 weeks developed forestomach hyperplasia, and forestomach papillomas and carcinomas, the same lesions observed in the two NTP studies.
>
> (3) NTP acknowledged that epichlorohydrin is a direct-acting mutagen and was a possible contributor to tumorigenic effects in the forestomach given that gavage administration can produce epichlorohydrin concentrations at the site of application similar to those in the drinking water study by Konishi *et al.* (1980), albeit for much shorter periods.
>
> If this is the case, and if epichlorohydrin was a contributor to forestomach tumors, it is reasonable to question the influence of epichlorohydrin in mouse lung tumors

[6] Memorandum from OEHHA Chief Deputy Director Allan Hirsch to DPR Assistant Director Marylou N. Verder-Carlos, "1,3-D, OEHHA Comments on DPR's Draft Risk Management Directive," dated September 20, 2016.

following inhalation exposure. This variable cannot be ruled out as a confounding factor for all other neoplastic lesions reported in rats and mice from the NTP studies. It is significant that the NTP studies reported various neoplastic lesions in multiple organs/tissues, while the other 6 bioassays that have been conducted for 1,3-D report only two tumor types, one in rats and one in mice. The clearly distinguishing difference between the NTP and non-NTP bioassays is the presence of epichlorohydrin as a stabilizer in the former and the presence of ESO in the latter.

(4) The purity of the 1,3-D in the NTP studies is also less than the other four oral cancer bioassays (92% vs 95~96%), further supporting that the studies were conducted on a different material than has been sold now for over 30 years.

(5) The NTP carcinogenicity study of 1,3-D in male mice was considered "inadequate" by NTP because of the low survival (8/50) in the male vehicle control group. In fact, 25 out of 50 vehicle control male mice died at weeks 48-51. Further, the mouse study failed to fully randomize the animals in their treatment groups.

(6) The fact that mortality in control male mice was higher than either of the treated male mice groups, coupled with the employment of only two treatment groups create a situation where dose-response analysis is virtually impossible for assessing possible treatment-related effects.

(7) The NTP studies were not conducted according to GLP.

(8) The dosing regimen in the NTP studies, *i.e.*, 3 days of test material administration per week, is clearly not in accordance with acceptable exposure protocol in guideline cancer bioassays.

(9) For all of the reasons above, the NTP (1985) cancer bioassay of 1,3-D in male mice should not be considered a reliable study for evaluating the carcinogenic potential of oral exposure to 1,3-D as it is currently manufactured.

OEHHA also commented that the Kelly study (1997) does not refute the lung tumors attributed to oral exposure to 1,3-D in the NTP cancer bioassay, due to differences in the strains of mice and experimental design (*e.g.,* 3 days/week, dose levels, diet). Relative to possible strain differences in lung tumor response, the oral gavage NTP study used B6C3F1 strain, while Kelly (1997) used CD-1 mice. Mouse lung tumors are not unique to the B6C3F1 strain; in CD-1 mice, the historical control incidence of male mouse lung tumors ranges from 8% to 61% (Cohen (2020).

High background incidence of lung adenomas in male B6C3F1 mice has been well recognized due to its genetic susceptibility. When the incidence of current cancer bioassay in B6C3F1 male mice was compared with historical control data from the Dow Toxicology Lab and NTP, the combined incidence in male mice at 60 ppm (44%) from the cancer bioassay is just outside the historical control range of the Dow Toxicology Lab (up to 38%) and NTP range (up to 42%), suggesting at most an equivocal tumorigenic potential of 1,3-D.

OEHHA has stated that the duration of the NTP study was 2 years and first lung tumor was observed at 78 weeks, while the Kelly study (1997) in-life duration was 18 months (77 weeks). The inference here is that the Kelly study (1997) could not have seen lung tumors because the exposure duration was too short. This perspective can be refuted as isoniazid given in the drinking water to CD-1 mice produced an increase in lung tumors in 2 months, and 100% lung tumors in 7 months, according to Cohen (2020). This example demonstrates that: (1) CD-1 mice are plenty susceptible to lung tumors, and (2) an 18-month study is of sufficient duration to detect an increase in lung tumors in CD-1 mice.

Finally, OEHHA stated that the dose levels were higher in the NTP study compared to the Kelly study (1997). The Kelly study utilized somewhat lower doses, i.e., about 1.7-fold, based on the gavage dose levels and weekly dosing schedule, (high dose of 100 mg/kg/day, 3 days per week for NTP vs. 25 mg/kg/day, 7 days per week for Kelly). However, the Kelly study (1997) high dose group (25 mg/kg/day) was sufficient to results in effects (e.g., body weight changes and histopathology in the rat study and histopathology in the mouse study), and the study design is consistent with recommended guidance (EPA 2005). The high dose in long-term studies is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects while not compromising the outcome of the study through excessive toxicity or inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms) (EPA 2005).

Further, the 3 days per week dosing regimen used in the NTP bioassay is not a standard or accepted approach; to the best of our knowledge, NTP has not used a 3 days per week dosing regimen since the late 1970s when its 1,3-D bioassay was actually performed. If the failure of the Kelly study (Kelly, 1997) to detect lung tumors is due to 7 days per week dosing, not 3 days per week, then cancer studies and assessments for vast numbers of chemicals would need to be reconsidered or even repeated, because so few of them were tested with a 3 days per week regimen.

VII. NSRLs Based on Recent DPR and US EPA Risk Assessments Would Be 50 and 400 Micrograms Per Day, Respectively

If deemed necessary by OEHHA to establish an NSRL, it is scientifically appropriate and straightforward to rely upon the recent risk assessments by DPR (2015) or US EPA (2020). Based on the DPR (2016) risk assessment, the NSRL would be 50 mcg/day. In comparison, the NSRL would be 400 mcg/day based on the EPA (2019) risk assessment. The key difference is that DPR used a linear extrapolation model and US EPA used a threshold model.

A. Both DPR and US EPA Relied On Lomax (1987) as the Critical Study For the Cancer Risk Assessment of Inhaled 1,3-D

1. Identification of the most sensitive study of sufficient quality

The mouse inhalation carcinogenicity study by Lomax (1987) in B6C3F1 mice is the most sensitive study of sufficient quality and the only positive inhalation study for 1,3-D upon which to assess and derive an NSRL if that is deemed necessary by OEHHA. The recent study by Bartels *et al* (2020) evaluated the toxicokinetics associated with tumors (observed only at the high dose

in male mice). This demonstrates that the increase in lung tumors was observed only at a concentration exceeding the KMD and that this exposure level is not relevant for quantitative risk assessment. The US EPA CARC (US EPA 2019) reached the same conclusion, as noted above. A description of the Lomax (1987) study follows below.

2. Experimental Design

Groups of 70 B6C3F1 mice of each gender were exposed by whole-body inhalation to target concentrations of 0, 5, 20, and 60 ppm 1,3-D, containing 91.1% 1,3-D (49.5% cis and 42.6% trans) for 6 hours per day, five days per week for 2 years. Ten mice/sex/exposure level were predesignated for interim sacrifice at 6 and 12 months of exposure. The remaining 50 mice/ sex/exposure level was designated for the oncogenicity portion of the study.

3. Non-Cancer Findings

There were no reported effects of treatment on mortality, clinical signs, hematology, clinical chemistry, or urinalysis. There was a statistically significant decrease in body weight gain in 60 ppm males (3–9%) and females (2–11%, only the first 5 months on study). Urinary bladder effects were noted primarily in females at 20 and 60 ppm (slight, moderate or marked roughened, irregular and opaque surfaces were reported in 20/50 at 20 ppm and 30/49 at 60 ppm compared with 3/50 slight in the control group). Hypertrophy and hyperplasia of the nasal respiratory mucosa (very slight/slight) were observed in most 60 ppm mice of both sexes and in 20 ppm females. Degeneration of olfactory epithelium (very slight/slight) was noted in most 60 ppm mice of both sexes. Hyperplasia of the epithelial lining of the non-glandular portion of the stomach was observed in 60 ppm males (0, 5, 20, and 60 ppm: males 0, 3, 1, and 8; females 0, 0, 0, and 2). The reported NOAEL was 5 ppm and the LOAEL was 20 ppm based on urinary bladder hyperplasia and hypertrophy/hyperplasia of the nasal respiratory mucosa.

4. Tumor Findings

A statistically identified increase in benign lung tumors (bronchioloalveolar adenomas) was observed only in male mice exposed to the highest concentration (60 ppm) of 1,3-D (22/ 50 vs. 9/50 in controls). Tables 3 and 4 summarize the male and female lung tumor incidences and statistical analysis from Lomax *et al* (1987).

Table 3: Carcinogenicity studies via inhalation exposure (from Yan *et al.*, 2020)

Study	Species/strain/duration	Concentration (ppm)	Tumor Type	Incidence (%)
1	Mouse / B6C3F1/ 2 years	0, 5, 20, 60	Bronchioloalveolar adenoma	M: 18, 12, 26, 44 F: 8, 6, 10, 6
2	Rat / F344 / 2 years	0, 5, 20, 60	None	Not tumorigenic

Study 1: Lomax et al. 1987 as in B.6.5.2.4 of Spain (2018) and Lomax et al. (1989).
Study 2: Lomax, 1987 as in B.6.5.1.5 of Spain 2018) and Lomax et al. (1989)

Table 4: Bronchioloalveolar tumor rates and statistics following two-year exposusre in B6C3F1 mice (from Yan *et al.*, 2020)

PPM	0	5	20	60
		Males		
Adenomas %	9 / 50 (18)	6 / 50 (12)	13 / 50 (26)	22 / 50 (44)
	< 0.001b**	0.2883c	0.2348	0.0044*

Table 4: Bronchioloalveolar tumor rates and statistics following two-year exposusre in B6C3F1 mice (from Yan *et al.*, 2020)				
Carcinomas %	0 / 50 (0)	13 / 50 (26)	22 / 50 (44)	0 / 50 (0)
	N / A	1	1	1
Combined %	9 / 50 (18)	6 / 50 (12)	13 / 50 (26)	22 / 50 (44)
	< 0.001**	0.2883	0.2348	.0044*
Females				
Adenomas (%)	4 / 50 (8%)	3 / 50 (6%)	5 / 50 (10%)	3 / 50 (6 %)
	N / A.	0.5	0.5	0.5
Carcinomas (%)	0 / 50	0 / 50	0 / 50	0 / 50
	N / A	1	1	1
Combined (%)	4 / 50 (8%)	3 / 50 (6%)	5 / 50 (10%)	3 / 50 (6%)
	N / A	0.5	0.5	0.5
*p<0.05; **p<0.01				
[a] Lomax et al. 1987 as in B.6.5.2.4 of Spain (2018) and Lomax et al. (1989) [b] Significance of trend denoted at control Significance of pair-wise comparison with control at dose level.				

B. The Regulatory Target Concentration Established by DPR in Its 2015 Cancer Risk Assessment Yields an NSRL of 50 Micrograms Per Day

DPR completed its Risk Characterization Document (RCD) for 1,3-D in December 2015. Based on this risk assessment, DPR set a regulatory target concentration of 0.56 parts per billion (ppb) of 1,3-D in the air as a 70-year average in order to achieve a risk goal of 1×10^{-5}.[7] Based on DPR's cancer risk assessment of 1,3-D, an inhalation NSRL of 50 mcg/day can be calculated, as described below.

A concentration of 0.56 ppb of 1,3-D in air may be converted to units of mcg/m^3 using the following conversion factor: 1 ppb = 4.54 mcg/m^3. Thus, an air concentration of 0.56 ppb of 1,3-D equals an air concentration of 2.5 mcg/m^3. The Proposition 65 regulations state that adults inhale 20 m^3/day of air as a default assumption. Based on the DPR risk assessment, the theoretical 10^{-5} risk of 1,3-D, expressed as mcg/day, is 50 mcg/day as shown in this formula:

$$\textbf{NSRL} = 2.5 \text{ mcg/m}^3 \times 20 \text{ m}^3\text{/day} = 50 \text{ mcg/day}$$

The methods and assumptions used to calculate this inhalation NSRL, based on DPR's risk assessment, are consistent with the requirements of Proposition 65. DPR used a linear multistage model to calculate the cancer potency of 1,3-D; the linear multistage model is the default model in the Proposition 65 regulations.

DPR considered that 1,3-D may cause cancer by two possible mechanisms: portal of entry or systemic modes of action. The DPR scientists evaluated both mechanisms and concluded that "the weight of the evidence favored a portal of entry mode of action based on currently available studies."[8] Although Proposition 65 assumes listed carcinogens have a systemic mode of action (based on the allometric scaling factors in Section 25703(a)(6)) as a default assumption), the regulations state that default assumptions are used in the absence of scientifically more appropriate

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[7] DPR Memorandum from Chief Deputy Director Teresa Marks to Assistant Directors Marylou Verder-Carlos and George Farnsworth, dated October 6, 2016. p. 3. Risk Management Directive and Mitigation Guidance for Cancer Risk from 1,3-Dichlorpropene.

[8] *Id.*, p. 2.

assumptions. In other words, Proposition 65 allows the use of allometric scaling factors based on a portal of entry mode of action when it is scientifically more appropriate, which is the determination made by DPR in its evaluation of 1,3-D.

Consistent with Proposition 65, DPR concluded that a cancer risk goal of 1 x 10^{-5} for a 70-year lifetime exposure was a reasonable objective for mitigation:

> "A cancer risk goal of 1 x 10^{-5} for a 70-year lifetime exposure means that the risk of contracting cancer should be no more than 1 individual for every 100,000 people. The risk level and exposure period are ***consistent with the Proposition 65 standards for notification of carcinogenic risk*** and with the U.S. EPA non-dietary cancer risk policy, which states that U.S. EPA will seek to reduce risks in the 10^{-4} to 10^{-6} range.[9]"

In summary, an inhalation NSRL of 50 mcg/day would be consistent with DPR's risk assessment of 1,3-D.

C. The RfD and RfC Established by US EPA in the 2019 CARC Risk Assessment Support NSRLs Greater Than 50 Micrograms Per Day

In 2019, US EPA's Cancer Assessment Review Committee reevaluated the carcinogenic potential of 1,3-D. In accordance with the US EPA's Final Guidelines for Carcinogen Risk Assessment (EPA 2005), the CARC classified 1,3-D as "Suggestive Evidence of Carcinogenic Potential based on the presence of liver tumors by the oral route in male rats only."[10] Given this finding, US EPA stated that "quantification of human cancer risk is not required." The CARC recommends using a non-linear approach (a reference dose (RfD)) that will adequately account for all chronic toxicity including carcinogenicity, that could result from exposure to 1,3-dichloropropene."[11] Using a non-linear threshold approach would result in a NSRL well above 50 mcg/day for 1,3-D.

The US EPA Reference Dose (RfD) and Reference Concentration (RfC) are based on the most sensitive non-carcinogenic chronic effects observed in animals exposed to 1,3-D orally and by inhalation, respectively.[12] Oral and inhalation NSRLs may be estimated.by assuming that the RfD and RfC, respectively, represent a threshold for carcinogenicity. US EPA's current RfD is 0.03 mg/kg/day based on the $BMDL_{10}$ for chronic irritation and a 100-fold uncertainty factor.[13]

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[9] Barolo D., Non-Dietary Cancer Risk Policy, Office of Pesticide Programs and Toxic Substances, U.S. EPA, August 14, 1996) (emphasis added).

[10] US EPA memorandum from Greg Akerman and Anwar Dunbar, CARC to Christine Olinger, Hope Johnson, and Cynthia Giles-Parker, p. 5, dated September 26, 2019.

[11] *Id.*

[12] US EPA IRIS 1,3-Dichloropropene (DCP) (CASRN 542-75-6) | IRIS | US EPA.

[13] *Id.*

Assuming the Proposition 65 default assumption of a 70 kg adult body weight, an oral NSRL is estimated to be 2100 mcg/day based on a threshold model.

US EPA's current Reference Concentration (RfC) is 0.02 mg/m^3 based on the $BMCL_{10}$ for hypertrophy/hyperplasia of the nasal respiratory epithelium and an uncertainty factor of 30.[14] Assuming the Proposition 65 default assumption that an adult inhales 20 m^3 of air per day, an inhalation NSRL is estimated to be 400 mcg/day based on a threshold model.

In summary, these calculations confirm that oral and inhalation NSRLs for 1,3-D based on a threshold model using US EPA's RfD and RfC would be well above 50 mcg/day.

VIII. An Alternative Approach Using a Benchmark Dose for Lung Tumors Would Result in NSRLs in The Range of 270 to 3100 Micrograms Per Day

We propose that OEHHA also consider an alternative threshold approach to developing a NSRL for 1,3-D that is based on a Benchmark Dose (BMD). Use of a BMD approach to define a Point of Departure (POD) for developing a NSRL for 1,3-D is appropriate because the BMD is independent of experimental study design. In the case of the RfC, a BMD was determined by US EPA for the most sensitive effect (*i.e.*, bilateral hypertrophy & hyperplasia of the nasal respiratory mucosa). For the alternative approach, a BMD_{01} is derived for 1,3-D based on bronchioloalveolar adenomas in male B6C3F1 mice exposed to 1,3-D by inhalation in the Lomax *et al.* (1987) study. The BMD_{01} is the estimate of the dose that causes a 1% increase in the tumor incidence.

The EPA Benchmark Dose Software, Version, 2.7 was used to run eight dichotomous models at a confidence limit of 0.95 and assuming extra risk. These models were: Gamma, Logistic, Log Logistic, Log Probit, Multistage-Cancer, Probit, Weibull, and Quantal-linear. The lung tumor data fit all eight models. The model with the lowest Aiaike's Information Criterion ("AIC") was the Probit model, which was presumed to be the best model that fit the data. The BMD_{01} of 2.38 ppm of 1,3-D was identified from the Probit model, and the lower bound confidence limit on this BMD_{01}, known as the $BMDL_{01}$, is 1.80 ppm. In comparison, the BMD_{01} and $BMDL_{01}$ based on the Multistage-Cancer model, which has a slightly higher AIC, is 2.09 ppm and 0.95 ppm, respectively. For purposes of determining the NSRL in this section, the BMD_{01} of 2.38 ppm and the $BMDL_{01}$ of 1.80 are used because the Probit model fit the data better than any of the other models.

To adjust the $BMDL_{01}$ of 1.80 ppm for the purity of the test material (92%) and for a long-term residential bystander exposure scenario, the following equation is used to adjust the $BMDL_{01}$:

$$\textbf{Adjusted } \mathbf{BMDL_{01}} = BMDL_{01} \times \text{purity} \times (6 \text{ hr}/24 \text{ hr}) \times (5 \text{ days}/7 \text{ days})$$
$$= 1.80 \text{ ppm} \times 0.92 \times (6 \text{ hr}/24 \text{ hr}) \times (5 \text{ days}/7 \text{ days})$$
$$= 0.296 \text{ ppm}$$

14 *Id.*

The adjusted $BMDL_{01}$ may be converted into units of mg/m^3 using a conversion of 1 ppm = 4.54 mg/m^3:

$$\mathbf{BMDL_{01}} = 0.296 \text{ ppm} \times 4.54 \text{ mg/m}^3 \text{ per 1 ppm}$$
$$= 1.34 \text{ mg/m}^3$$

Using the default Proposition 65 assumption that a human inhales 20 m^3/day of air, the $BMDL_{01}$ expressed as mg/m^3 may be converted into units of mg/day:

$$\mathbf{BMDL_{01}} = 1.34 \text{ mg/m}^3 \times 20 \text{ m}^3\text{/day}$$
$$= 26.8 \text{ mg/day}$$

Finally, the $BMDL_{01}$ can be converted to an NSRL by application of a safety (or uncertainty) factor of 100, to account for inter-and intra-species variability and sensitivity:

$$\mathbf{NSRL} = \mathbf{BMDL_{01}} \div 100$$
$$= 26.8 \text{ mg/day} \div 100$$
$$= 0.268 \text{ mg/day (rounded up to 270 mcg/day)}$$

Thus, an NSRL of 270 mcg/day is calculated using the $BMDL_{01}$ for lung tumors and using a 100-fold uncertainty factor (Table 5).

To summarize, the following are the key elements of the proposed approach:

- Bronchioloalveolar adenoma tumor incidence in the male mouse is the endpoint that should serve as a basis for the BMD_{01}, which is the proposed Point of Departure (POD) for quantifying the NSRL.

- The most appropriate study for BMD modeling is Lomax (1987), which reported benign lung tumors in male mice only.

- The $BMDL_{01}$ (95^{th} percentile lower bound on the 1% BMD) provides a conservative and scientifically sound estimate of a practical threshold for this endpoint.

- The Probit Model has the best fit to the dose-response data from the lung tumor results.

- The $BMDL_{01}$ is adjusted for the purity of the test material and for difference between the pattern of exposure of male mice to 1,3-D in the Lomax (1987) study and the continuous long-term exposure of a human residential bystander.

- A 100-fold uncertainty (safety) factor is appropriate and conservative to apply to the $BMDL_{01}$ to account for inter- and intra-species sensitivity, especially since the lung tumors are due to a portal of entry exposure.

The estimated NSRL of 270 mcg/day is very conservative, for several reasons. First, it uses the $BMDL_{01}$, which is the 95% lower bound of the BMD_{01}, rather than the BMD_{01} itself, which is regarded as the "best" estimate of the dose that produces a 1% increase in tumors. If the BMD_{01} of 2.38 ppm is used, the NSRL would be 350 mcg/day (Table 5).

Second, the calculated NSRL does not assume that 1,3-D cause lung tumors via a portal of entry mechanism. If the RGDR of 3.44, which was used by EPA to account for portal of entry, had been employed to calculate the NSRL, the NSRL would be 3.44 times greater. In other words, adjusting for portal of entry and still using $BMDL_{01}$ and the 100-fold uncertainty factor, the NSRL would be 930 mcg/day (Table 5).

Third, as EPA notes, a total uncertainty factor or only 30 is appropriate when the RGDR is used. Thus, using the $BMDL_{01}$, the RGDR of 3.44, and an uncertainty factor of 30, the NSRL would be 3100 mcg/day (Table 5).

Table 5. Range of potential NSRLs for 1,3-D using a threshold approach based on the BMD_{01} or $BMDL_{01}$ for benign lung tumors in male mice

Point of Departure	Adjusted for purity of 1,3-D?	Adjusted for pattern of exposure?	Adjusted for portal of entry?	Uncertainty Factor	NSRL (mcg/day)
$BMDL_{01}$	Yes	Yes	No	100	270
$BMDL_{01}$	Yes	Yes	No	100	350
$BMDL_{01}$	Yes	Yes	Yes	100	930
$BMDL_{01}$	Yes	Yes	Yes	30	3100

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X. Appendix A

A. Genotoxicity (Badding *et al.*, 2020)

In vivo mutagenicity evaluation of the soil fumigant 1,3-dichloropropene (Badding et al 2020)

"This study investigated the effect of 1,3-D on mutant frequency (MF) at the *cII* gene in liver and kidneys from male transgenic Fischer 344 Big Blue® rats. The Big Blue® assay is a Transgenic Rodent (TGR) mutation assay described in OECD Test Guideline (TG) 488 (OECD 2013).

Twenty-four F344 homozygous Big Blue® male rats (six/group) were exposed daily to the test substance or placebo (sucrose microcapsules) mixed in diet, for four consecutive weeks, at target dose levels of 0, 12.5, 25, or 50 mg/kg/day. The placebo or test substance mixed in basal diet (TEKLAD Global Diet #2018CM) was provided *ad libitum* for 28 consecutive days of feeding. Animals were switched to normal, untreated diet on day 29. All study animals were terminated on day 31; a full necropsy was not performed, but the liver, kidneys, testes, lungs, bone marrow (femur), and forestomach were collected and stored frozen. Liver and kidney tissue samples from the first five rats/group were processed for DNA isolation and analyzed for *cII* mutants. DNA isolated from previously frozen liver and kidney tissues of N ethyl-N-nitrosourea (ENU; CAS no. 759 73-9) treated rats was used as a packaging positive control agent.

All animals survived to their scheduled termination, with no toxicologically relevant differences noted in the clinical observations between the placebo and test substance-treated animals. Total body weight gain (days 1–31) for the high dose group was 25% lower as compared to the placebo group, which correlated with lower food consumption values during the last two weeks of exposure.

No statistically significant differences were noted in the MF data when test substance-treated groups were compared to the placebo group, for either liver or kidneys. The positive control treatment with ENU produced a greater than threefold increase (statistically significant) in MF for both tissues tested, demonstrating the utility of the test system to detect induced mutants following exposure to a known direct-acting mutagen. The study design and results obtained met protocol-specified assay acceptance criteria and were consistent with the study requirements of OECD Testing Guideline 488 for TGR mutation assays."

B. Oncogenicity Studies (Kelly, 1997; Kelly, 1998)

Two additional carcinogenicity studies (Kelly 1997; Kelly 1998) via oral exposure recently became available to Dow, and are directly relevant to the present discussion surrounding NSRL derivation. These studies coupled with other oral bioassays for 1,3-D support the CA DPR and EPA's consideration that the high dose of 1,3-D induced lung tumors via inhalation exposure is indeed a portal of entry effect (discussed in more detail below).

Study descriptions

1. Kelly, C.M. (1998) A Chronic Toxicity and Oncogenicity Study with DD-92 in the Rat via Oral Gavage Administration.

Experimental Design: Groups of Sprague Dawley Crl:CD rats (50/sex/dose) were administered DD-92 in corn oil by oral gavage (5 mL/kg dose volume) at dosages of 0, 2, 10 and 25 mg/kg bw/day for up to 23 (males) or 24 (females) months (75/sex/group).

Non-cancer findings: There were no treatment-related increases in mortality in either sex.

Cumulative mortality for the 0, 2, 10 and 25 mg/kg/day groups was 34, 17, 32 and 22% for males and 24, 28, 31 and 38% for females, respectively. The body weights and body weight gains of male rats at 25 mg/kg bw/day were statistically significantly lower than controls beginning at Weeks 12 and 9 (5% lower body weight gain compared with controls), respectively, through to Week 72 (11% lower body weight gain compared with controls) of study. No treatment related alterations in clinical chemistry, urinalysis, organ weight, and gross pathology were observed.

The most significant findings were histopathological changes in the forestomach related to the gavage administration of the test material, most prominent at the 12 month time-point at 10 and 25 mg/kg bw/day.

Tumor findings: No treatment-related increases of tumors were identified.

2. Kelly, C. M. (1997) An Oncogenicity Study with DD-92 in the Mouse via Oral Gavage Administration.

Experimental Design: Groups of CD-1 mice (65/sex/group) were administered with DD-92 in corn oil by oral gavage at doses of 0, 2, 10 and 25 mg/kg bw/day for at least 18 months.

Non-cancer findings: No treatment-related increases in mortality in either sex were observed. No treatment related clinical signs, body weight, clinical chemistry, organ weight and gross pathology were noted. The only observed histopathology effects were in the urinary bladder of females at 25 mg/kg bw/day. The changes included transitional cell hyperplasia, chronic active inflammation, lymphoid cell infiltrate/aggregate, hyaline change of the lanima propria, stromal hyperplasia and hypertrophy, and accumulation of brown pigment in reticuloendothelia cells.

Tumor findings: A slightly increased incidence of benign submucosal mesenchymal tumors was observed in females at 25 mg/kg bw/day (0/65, 0/63, 0/61, and 3/65 for control, low-, mid- and high-dose groups, respectively). However, the general consensus among pathologists is that mesenchymal proliferative lesions do not represent true neoplasia (Frazier et al., 2012). Thus, no treatment-related increases of tumors were identified.

C. Weight of Evidence Analysis of the Tumorigenic Potential of 1,3-Dichloropropene Supports a Threshold-Based Risk Assessment (Yan *et al.*, 2020)

"1,3-Dichloropropene (1,3-D; CAS #542-75-6) is a fumigant used for preplant treatment of soil to control parasitic nematodes and manage soil borne diseases for numerous fruit, vegetable, field and tree and vine crops across diverse global agricultural areas. In the USA, 1,3-

D has historically been classified by the U.S. EPA as likely to be carcinogenic to humans via both oral and inhalation routes. This classification for the oral route was primarily based upon increases in multiple tumor types observed in National Toxicology Program (NTP) cancer bioassays in rats and mice, while the classification for the inhalation route was based upon increased benign bronchioloalveolar adenomas in a mouse study conducted by The Dow Chemical Company. Based on U.S. EPA standard risk assessment methodologies, a low-dose linear extrapolation approach has been used to estimate risks to humans. Furthermore, genotoxicity associated with 1,3-D was historically considered a potential mode of action (MOA) for its tumorigenicity. New information is available and additional studies have been conducted that reveal a different picture of the tumorigenic potential of 1,3-D. These data and information include: (1) initial cancer studies by the NTP were conducted on an obsolete 1,3-D product which contained a known mutagen/carcinogen, epichlorohydrin, as a stabilizer while current 1,3-D fumigants use epoxidized soybean oil (ESO) as the stabilizer; (2) results from two additional oral rodent cancer bioassays conducted on the current 1,3-D product became available and these two studies reveal a lack of carcinogenicity; (3) a newly conducted Big Blue study in F344 rats via the oral route further confirms that 1,3-D is not an *in vivo* genotoxicant; and (4) a newly conducted repeat dose inhalation toxicokinetic (TK) study shows that linear dose proportionality is observed below 30 ppm, which demonstrates the non-relevance of 60 ppm 1,3-D-induced benign lung tumors in mice for human health assessment. This weight of evidence review is organized as follows: (a) the TK of 1,3-D are presented because of relevant considerations when evaluating test doses/concentrations and reported findings of tumorigenicity; (b) the genotoxicity profile of 1,3-D is presented, including a contemporary study in order to put a possible genotoxicity MOA into perspective; (c) the six available bioassays are reviewed followed by (d) scientifically supported points of departure (PODs) and evaluation of human exposure for use in risk assessment. Through this assessment, all available data support the conclusion that 1,3-D is not a tumorigen at doses below 12.5 mg/kg bw/day via the oral route or at doses below 30 ppm via the inhalation route. These findings and clearly identified PODs show that a linear low dose extrapolation approach is not appropriate and a threshold-based risk assessment for 1,3-D is human health protective. Finally, in 2019, the Cancer Assessment Review Committee (CARC; US EPA, 2019) reevaluated the carcinogenic potential of 1,3-D. In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment, the CARC classified 1,3-D (Telone) as "Suggestive Evidence of Carcinogenic Potential based on the presence of liver tumors by the oral route in male rats only." Given this finding, EPA stated that "quantification of human cancer risk is not required. The CARC recommends using a non-linear approach (i.e. reference dose (RfD)) that will adequately account for all chronic toxicity including carcinogenicity, that could result from exposure to 1,3-dichloropropene."

D. Peer Review of a Cancer Weight of Evidence Assessment Based on Updated Toxicokinetics, Genotoxicity, and Carcinogenicity Data for 1,3- Dichloropropene using a Blinded, Virtual Panel of Experts (Hays *et al.*, 2020)

An independent peer review of the Yan *et al* (2020) weight of evidence analysis was conducted, and the abstract is reproduced here (Hays *et al.*, 2020):

"A cancer weight of evidence (WOE) analysis based on updated toxicokinetics, genotoxicity, and carcinogenicity data for 1,3-dichloropropene was peer reviewed by a panel of

experts. Historically, 1,3-dichloropropene has been classified in the U.S. as "likely to be carcinogenic to humans" via oral and inhalation exposure routes based upon the results of rodent cancer bioassays conducted in the 1980s. Contemporary studies led the authors of the WOE analysis to conclude that the currently manufactured form of 1,3-dichloropropene is not mutagenic and not carcinogenic below certain doses, pointing to a threshold-based approach for cancer risk assessment. SciPinion conducted a peer review of the WOE analysis using methods for assembling and managing blinded expert panels that maximize expertise while minimizing potential selection/participation bias. The process was implemented through a web-based application that poses a series of questions soliciting the experts' scientific opinions and observations about specific topics. The goal of the peer review was to have experts provide conclusions about the WOE for carcinogenicity classification of 1,3-dichloropropene, identify potential data gaps, and evaluate the validity of a threshold-based risk assessment for 1,3-dichloropropene. Based on a robust peer review of the current scientific information, a cancer WOE classification of "not likely to be carcinogenic to humans" is best supported for 1,3-dichloropropene. This conclusion is reached with a high degree of consensus (consensus score ¼ 0.92) across expert panel members."

E. Metabolic Basis for Nonlinearity in 1,3-Dichloropropene Toxicokinetics and Use in Setting a Kinetically-derived Maximum Inhalation Exposure Concentration in Mice (Bartels *et al.*, 2020)

"1,3-Dichloropropene (1,3-D) showed a statistically increased incidence of bronchioloalveolar adenomas in male B6C3F1 mice at 60 ppm air concentration during previous chronic inhalation testing. No tumors were observed in female mice, nor in either sex of F344 rats up to 60 ppm, the highest dose tested. Therefore, to understand if lung tumors observed in high dose male mice are due to saturation of metabolic clearance, the linearity of 1,3-D concentrations in mouse blood was investigated on day 15 of repeated nose-only inhalation exposure to 0, 10, 20, 40, 60, 90, and 120 ppm (6 h/d, 7 d/week). Additional groups were included at 20, 60, and 120 ppm for blood collection at 1.5 and 3 h of exposure and up to 25 or 40 min post-exposure to determine area under-the-curve. The data provide multiple lines of evidence that systemic exposures to 1,3-D in the mouse become nonlinear at inhalation exposure levels of 30 ppm or above. A reduction in minute volume occurred at the highest exposure concentration. The glutathione (GSH)-dependent metabolism of 1,3-D results in significant depletion of GSH at repeated exposure levels of 30 ppm and above. This loss of GSH results in decreased metabolic clearance of this test material, with a concomitant increase of the 1,3-D isomers in circulating blood at exposure concentrations 30 ppm. Shifts in the ratio of cis- and trans-1,3-D also support nonlinear toxicokinetics well below 60 ppm. Based on this data, a kinetically derived maximum dose for 1,3-D in mice for repeated exposures should be at or below 30 ppm. These results support non-relevance of 1,3-D-induced benign pulmonary tumorigenicity in mice for human health risk assessment."

F. Relevance of Mouse Lung Tumors to Human Risk Assessment (Cohen *et al.*, 2020)

"Mouse lung is a common site for chemical tumorigenicity, but the relevance to human risk remains debated. Long-term bioassays need to be assessed for appropriateness of the dose, neither exceeding Maximum Tolerated Dose (MTD) nor Kinetically based Maximum Dose

(KMD). An example of the KMD issue is 1,3-dichloropropene (1,3-D), which only produced an increased incidence of lung tumors at a dose exceeding the KMD. In addition, since mouse lung tumors are common (>1% incidence), the appropriate statistical significance is $p < .01$. Numerous differences exist for mouse lung and tumors compared to humans, including anatomy, respiratory rate, metabolism, tumor histogenesis, and metastatic frequency. The recent demonstration of the critical role of mouse lung specific Cyp2 F2 metabolism in mouse lung carcinogenicity including styrene or fluensulfone indicates that this tumor response is not qualitatively or quantitatively relevant to humans. For non-DNA reactive and non-mutagenic carcinogens, the mode of action involves direct mitogenicity such as for isoniazid, styrene, fluensulfone, permethrin or cytotoxicity with regeneration such as for naphthalene. However, the possibility of mixed mitogenic and cytotoxic modes of action cannot always be excluded. The numerous differences between mouse and human, combined with epidemiologic evidence of no increased cancer risk for several of these chemicals make the relevance of mouse lung tumors for human cancer risk dubious."